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Liquisolid Compact Technique for Improvement of the Dissolution Rate: A Review

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Review Article

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Abstract: The liquisoid compact technique is a promising technique to enhancing the dissolution of poorly water soluble drugs. About 40% of newly discovered drugs are poorly water soluble or water insoluble categories. Simple processing low cost and great potentials in industrial production are the main advanges of this technique. By using this technique, the liquid medications such as solutions or suspension of water insoluble drug can be easily converted in to powder with acceptable flow properties using suitable powder excipient. This review article is focused the formulation of liquisolid systems, classification of liquisolid systems, evaluation and its applications in the field of pharmaceutical sciences.

Keywords: liquisolid compact, poorly soluble drug, coating material, formulation and evaluation.

INTRODUCTION

The limited solubility of drugs is a one of the challenging issue for industry, during the development of the ideal solid dosage form unit. Solubility is the important parameter for oral bioavailability. Different techniques are employed to enhance the dissolution of poorly soluble drugs like use of water-soluble salts and solid dispersion, increasing surface area by reducing particle size, pH adjustment, microencapsulation, co-precipitation, lyophilization, inclusion of drug solutions or liquid drug in to soft gelatin capsule, solubilisation in a surfactant system [1].

Liquisolid compact technique is a novel and a successful tool to improve the solubility and dissolution of poorly water soluble drugs and consequently bioavailability [2]. The liquisolid technique is applied to formulate liquid medications (i.e, oily liquid drugs, suspensions or emulsion of water-insoluble solid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting [3].

The liquisolid compact system (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, non-adherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier(cellulose, starch, lactose etc..) and coating materials(silica) [4].

The liquisolid systems, even the drug might be in a solid dosage form, it is held within the powder substrate in solution or in a solubilized, almost molecularly dispersed state. Due to their significantly increased wetting properties and surface area of drug is available for dissolution, liquisolid compacts of water-insoluble substances is expected to display enhanced drug release characteristics and consequently improved oral bioavailability [5].

CONCEPT

The drug is dissolved in the liquid vehicle and incorporated into a carrier material which has a porous surface and closely mattered fibre in its interior such as cellulose; both absorption and adsorption take place. The liquid initially absorbed from the interior of the particle is captured by its internal surface. After saturation, adsorption of the liquid onto the internal and external surface of the porous carrier particle. Then, the coating material provides high adsorptive properties and large surface area which gives the desirable flow characteristics [6]. In liquisolid system, the drug is in solution form in liquid vehicle, and at the same time, it is carried by power.

The wettability is one of the mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates decreasing the interfacial tension between dissolution medium and tablet surface [6]. When increasing the wettability and effective surface area for dissolution, liquisolid compacts may be

expected to produce enhanced release profiles of water-insoluble drugs. Dissolution of a non-polar drug is one of the rate limiting step in gastrointestinal absorption, and the orally administered water-insoluble drug is in solution form, it produces better bioavailability and thus displaying enhanced dissolution rates [6,7] (fig.1)

The drug release depends on the characteristics of drug, carrier and vehicle use. If any changing these variables, liquisolid technique can be used for enhancing or retarding the drug release [6, 7].

Advantage

- Production cost is low compared to soft gelatin capsules.
- It is specifically for powdered liquid medications.
- Optimized sustained release.
- It is used in controlled drug delivery systems.
- To minimize excipients in formulation compare to other formulations.
- Industrial production is also possible.
- Enhance bioavailability.
- Omit the process approaches like nanonisation, micronization technique [8].

Disadvantage

- Formulation of high dose lipophilic drugs the liquisolid tablet is difficult.
- High level of coating materials and carriers are required to maintain flowability and compatibility.
- When increases the weight of each tablet above 1gm which is very difficult to swallow.
- Acceptable compression properties may not be achieved during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness [9].
- Mathematical calculations are required.

Classification of liquisolid system

A. Based upon the type of liquid medication contained

- Powdered drug solutions.
- Powdered drug suspensions.
- Powdered liquid drugs.
- Based upon the formulation techniques used
- Liquisolid compacts.
- Liquisolid microsystems.

Powdered drug solution

This preparation is not a solvent deposition technique so it does not involve drying or evaporation. since non-volatile solvents are used to prepare the drug solution or suspension, the liquid vehicle does not evaporate and the drug is carried within the liquid system which in turn, is dispersed throughout the final product based upon the consistency of the powder substrate, the quantity of solid drug dispersed in the liquid medication and the physicochemical properties of the liquid vehicle used the acceptable liquid-to-powdered percent ratio will range from 2 to 52 [10].

Powdered liquid drugs

The first two may be produced by conversion of drug solutions or (prednisolone solution in propylene glycol) or drug suspensions (e.g. gemfibrozil suspension in polysorbate 80), and the latter from the formulation of liquid drugs (e.g.clofibrate, valproic acid, liquid vitamin, etc.), in to liquisolid systems [10].

Liquisolid microsystems

It is refers to the capsules is prepared by combining the drug with a coating material and with a carrier together with the inclusion of an additives example: PVP in the liquid medication wherein the resulting size may be as much as 5 times that of liquisolid [10].

Liquisolid compact system

The powder is retaining only limited amount of liquid while maintaining acceptable flow and compression properties. Liquisolid compacts are prepared using previously outlined method to produce tablets or capsules, whereas the liquisolid micro systems are based on a new concept which to produce an acceptably flowing admixture for encapsulations [10].

Componants of liquisolid compact

Ideal characteristics of components of liquisolid compact

- Drug: poorly soluble, insoluble, liquid or lipophilic, solubility in high boiling point, water miscible solvent.
- Carrier: good compressibility, coarser granular.
- Coating materials: high surface area, good adsorptive properties.
- Non-volatile solvent: water miscible, hydrophilic or lipophilic.

Main four components of liquisolid compacts are follows

- Non-volatile solvent
- Disintegrant
- Carrier material
- Coating material

Non-volatile solvent

It should be inert, high boiling point, water soluble and not highly viscous organic solvent systems and having ability to solubilize the drug. The non-volatile solvent is act as a binding agent in the liquisolid formulation. Various non-volatile solvents are used in liquisolid systems include polyethylene glycol 200 and 400, glycerine, polysorbate 80, propylene glycol [10,11].

Disintegrants

Disintegrants increases the rate of drug release, water solubility and wet ability of liquisolid granules.

Mainly used disintegrants are crospovidone and sodium starch glycolate [10,11].

Carrier materials

It should be porous material produce sufficient absorption properties which contribute in liquid absorption. The carrier material can retain only certain amounts of liquid and it maintain acceptable flow and compression properties. When increasing the moisture contents of carrier material it will decrease powder flowability. E.g. microcrystalline cellulose such as avicel PH 102 and avicel PH 200, 20 [10, 11].

Coating Material

Coating material is required for covering the surface and maintains the powder flowability. It covering the wet carrier particles and displaying a drylooking powder by adsorbing any excess liquid. Coating material include silica, aerosil200 and syloid [10,11].

Mechanism

Three main mechanism are involved for enhancement of drug release they are,

Increased drug surface area

The surface area of drug available for drug release is much greater than that of drug particles within directly compressed tablets. The drug present in the system is completely dissolved in liquid vehicle and present in powdered substrate in solubilized, and molecularly dispersed state [12].

When increasing the drug content, the solubility limits also increases and increasing the fraction of undissolved drug in the liquid vehicle and release rate decreases. In liquisolid system release rate of drug is directly proportional to the fraction of the molecularly dispersed drug [13].

Increased aqueous solubility of the drug

The small amount of liquid vehicle in liquisolid system is not sufficient for increase the solubility of drug in aqueous dissolution medium. If the small amount of liquid vehicle act as a co-solvent and this less amount of vehicle is sufficient to increase the aqueous solubility of poorly soluble drug [14].

Increased wettability

The non-volatile solvent present in the liquisolid system produce wetting of drug particles by decreasing the interfacial tension between tablet surface and dissolution medium. So the contact angle of liqusolid system is lowered when compared with conventional formulation thus improved wettability [15]. (fig. 2)

Method of preparation of liquisolid compact

Accurately weighed the calculated quantities of drug and non-volatile solvent in 20ml glass beaker and then heated to dissolve the drug in that solvent. Then the hot medication is incorporated into calculated quantities of carrier and coating materials. Mixing process is carried out by three steps. During the first stage, the system is blended at approximate mixing rate for one minute in order to evenly distribute liquid medications in the powder. In the second stage, the liquid/powder mixture is spread as a uniform layer on the surfaces of a mortar and standing for 5 min to allow drug solution to be absorbed in the interior of powder particles. In the third stage, the powder is scraped from the mortar surface by using aluminium spatula and then blended with sodium starch glycolate for another 30 seconds in similar way. It gives liquisolid formulation to be compressed [16]. (Fig. 3)

Evaluation of liquisolid compact

Precompression Studies

Flowability of liquisolid admixture is important for formulation of tablet dosage form. Therefore, it is very essential for study the flowability of these liquisolid powder admixtures prior to compression. Flowability can be evaluated by using various parameters such as Carr's index, angle of repose, and Hausner'sratio [17].

- **Angle of Repose**:
  The angle of repose of powder blend was determined by using fixed height funnel method. Angle of repose (θ) was calculated using the following equation:
  $$\Theta = \tan^{-1} h/r$$

Where "h" and "r" are the height and radius of powder cone [17]

- **Compressibility Index**
  Carr's compressibility index methods are mainly used to determining the compressibility index of the powder blend .The formula for Carr's index is as below [11].

Carr's index (%) = [(Tapped density − Bulk density) × 100] /Tapped density

- **Hausner'sRatio**
  Hausner's ratio was calculated from the equation [17].

  Hausner's ratio = Tapped density /Bulk density

Post Compression Evaluation

- Content of uniformity
- Weight variation
- Hardness
- Friability
- Disintegration
- In-vitro dissolution studies.

Tablet dimensions

Thickness and diameter of the liquisolid compact were measured by using vernier calliper. Three tablets from each formulation were used, and average values were calculated [18].

Tablet hardness

Tablets have a sufficient hard to resist breaking during normal handling and disintegrate properly after swallowing. It is used to measure of mechanical strength. The hardness of the liquisolid compacts was evaluated using Monsanto hardness tester. It is expressed in kg/cm2[18].

Friability

Tablet hardness is not an indicator for strength since some formulations compressed into very hard tablet tend to cap on attrition and losing their cap portions. Therefore friability is the method for measuring the tablets strengths. Roche friabilator was used for testing the friability. 20 tablets were weighed and placed in the Roche friabilator, and apparatus was rotated at 25 rpm for 4 min. After revolutions, the tablets were deducted and weighed again [18, 19].

Weight variation test

The weight variation test is used measure to ensure if the tablet contains the proper amount of drug. Weight variation test was performed as per IP 2007. 20 tablets were selected randomly and weighed. Average weight of the tablet was also determined. Not more than the two of the individual weights deviate from the average weight by more than 5% percentage deviation [18,19].

Drug content uniformity

Twenty tablets were selected randomly and average weight was calculated. Then the tablets were crushed by using a mortar and accurately weighed amount of average tablet were taken from the crushed blend. Then, the samples was transferred to 100 ml volumetric flasks and then diluted up to the mark with using methanol. The content was shaken periodically and kept for one hour for dissolving the drug completely. Then the mixtures were filtered and appropriate dilutions were prepared. The drug content in each tablet was estimated at λmax238 nm against blank reference [18,19].

The drug content uniformity was calculated using the following formula,

Practical Yield=Absorbance/slope×Dilution Factor

% Drug content=Practical yield/Theoretical yield×100

In vitro disintegration time

The in vitro disintegration time of a tablet is determined by using disintegrating apparatus as per I.P. specification.

I.P. specification: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 1.2 pH buffer maintained at 37°C ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles/min [19].

In vitro dissolution studies

In vitro dissolution study was carried out for 1 hour by using USP type 2 (paddle) method with 900ml of 0.1 N HCl and distilled water as the dissolution media at required rpm and 37°C+0.5°C. 10 ml of the sample was withdrawn and filtered at periodic time intervals in minutes. 10ml fresh dissolution fluid is replaced to the baskets to maintain the constant volume (sink condition). The filtered samples are analysed by using UV/Visible spectrophotometer [19].

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry is used to determine the interaction between excipients used in the formulation. This will also indicate the success of stability studies. When the drug is in the form of solution in liquisolid formulation it is the indication of complete disappearance of characteristic peaks and hence it is molecularly dispersed within the system [19].

X-ray diffraction (XRD)

The X-ray diffraction (XRD) patterns are used to determining for drug, excipient used in formulation, physical mixture of the drug and excipient, finally for the liquisolid system. It measures the disappearance of constructive specific peaks of drug in the liquisolid formulation and retaining peaks of carrier material. It also indicates that the drug entirely converted from crystalline to amorphous form or in solubilized form in the liquisolid formulation. The amorphization or solubilization of drug in the liquisolid system contributes the consequent improvement in the apparent solubility and also the dissolution rate of the drug [19, 20].

Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. When the peaks present in drug formulation and absence of extra peaks indicates that there is no chemical interaction. The prepared liquisolid compact were subjected to FT-IR analysis and approximately minimum quantity of less than 4mg was subjected to this analysis [19, 20].

PHARMACEUTICAL APPLICATION

- Rapid release rate is obtained in liquisolid compact.
- It is mainly used for water insoluble solid drugs or liquid lipophilic drugs.
- Solubility and dissolution improvement.

Liqusolid technique has widely used to improve the dissolution rate of low soluble drugs

(prednisolone, famotidine, valsartan, ketoprofen, clonazepam, etc.)[21]. The incorporation of high dose water in-soluble drugs into the liquisolid system by adding additives (PVP, HPMC and poly ethylene glycol) have the capability to increase the liquid absorption capacity of carrier and coating materials [22]. When load high dose of poorly water-soluble drugs into liquisolid system it will enhances the surface area and higher absorption capacity [23]. liquisolid compact technique was applied to enhance the dissolution rate of hydrochlorothiazide in comparison with solid dispersion technique [24]. The reduction of particle size and crystallinity and an enhancement of the wettability are the main mechanism for enhanced dissolution rate of tadalafil [25].

- **Designing of sustained release tablets**

It is a promising technique for preparing sustained release formulations of different drugs [26]. A main advantage of applying liquisolid technique prolonging drug release is the possibility to attain zero order release kinetics [27]. Sustained release formulation is designed to release drug in predetermined rate for a certain period [27]. Main limitation is high tablet weight, it attributed to the high dose of drug used in the sustained release liquid medications [28]. The polysorbate 80 (Tween 80) plays an important role in sustained drug release. The plasticizer effect of Tween 80, glass transition temperature (Tg) of polymer that applied in the formulation could be reduced. Here the polymer chains coalescence better, which produce fine polymer network with low porosity and high tortuosity. During release period the drug surrounded and restricted by fine network and it prolong the release [29]. The presence of non- volatile co-solvent was crucial for prolonging dug release. The sustained release action of HPMC was amplified and release is achieved by changing the type of co-solvent [30]. The solubility of drug in liquid vehicle had a significant role on drug release profiles. Physicochemical properties such as formation of micelles, HLB and dielectric constant also affect the drug release [31].

- **Minimize the influence of pH variation on drug release**

The solubility of weak acid and weak base is directly dependent on the ionization constant of the compound and pH of the environment. The dissolution and bioavailability of these drugs influenced by the pH of gastrointestinal fluids. It then lead to a high degree of inter and intra variability in drug bioavailability and therapeutic effects [32]. A poorly soluble weak base (mosapride citrate) liquisolid tablets, it minimize the effect of pH variation on drug release along the gastrointestinal tract with bio- relevant media [32]. Using liquisolid technique to minimize the pH variation on the release of loratidine [33].

- **Improve drug photo stability in solid dosage forms**

Loss of drug potency during photodegradation may result toxic degradation and cause potential side effect. Photostability study is one of the part of pre-formulation studies for photosensitive drugs [34]. Photo protective action of liquisolid technique mainly based upon the photo protective property of silicon dioxide due to its high refractive index [35]. The photo protective effect of liquisolid tablets was inversely proportional to the excipient ratio (R). Liquisolid technique was proved to be a promising alternative to conventional coating for improving drug photostability in solid dosage forms. This technique has exhibited great potential in reducing the effect of pH variation on drug release and also improving the photostability in solid dosage forms [36].

- **Bioavailability enhancement**

Due to significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts display enhanced drug release properties, and improved bioavailability.

- **Flowability and compressibility**

Excipients possessing large surface areas, fine particle size and granular grades produce good flow and compression properties. Drug existed in a molecular state of subdivision and systems are free flowing. Non-adherent, dry looking powders.

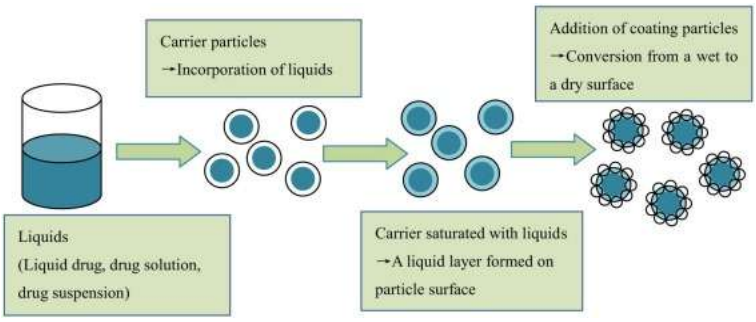

Fig-1: Concept of Liquisolid Compact

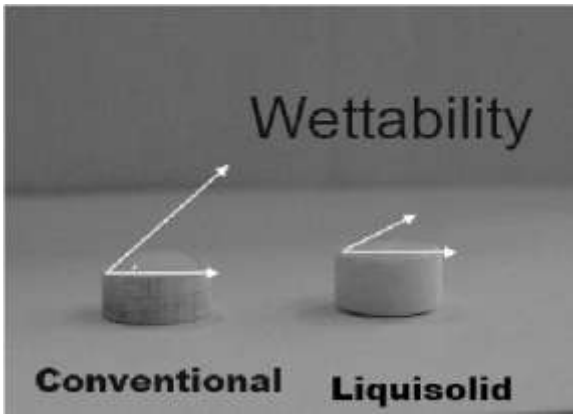

Fig-2: mechanism of increased wettability

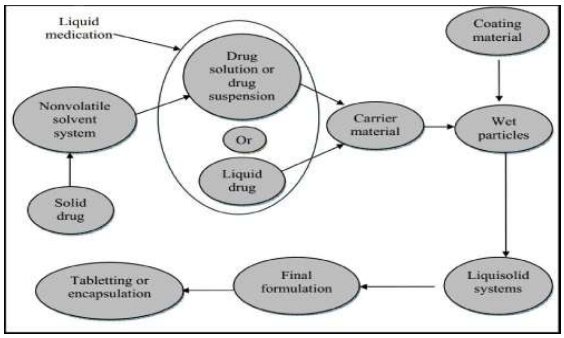

Fig-3: Method of Preparation

CONCLUSION

Enhancement of solubility and dissolution rate of poorly water soluble drugs is a major challenge for pharmaceutical scientists. Several techniques have been reported to improve drug solubility, among the liquisolid compact technique is one of the most promising approaches. This technique is also used to design sustained release dosage forms. Highest drug release rates are observed in liquisolid compact system and this system may be optimized by selection of liquid vehicle and carrier and coating materials. Finally this review is concluded that, various techniques are involved for the drug bioavailability enhancement, and this technique is the most promising approaches because it's simplified manufacturing method, cheaper production costs and also the prospect of industrial scale up due to the good flow and compaction properties.

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